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Term	Documents
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ADENOVIRUS	34981
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(4 AND (ADENOVIRUS OR VECTOR)).PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD.	46
(L4 AND (VECTOR OR ADENOVIRUS)).PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD.	46

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L4	L2 not L3	66	L4
L3	L2 and (hyperlipidemia and cholesterol)	19	L3
L2	(truncated or variant or fragment or deleted) same (apoE3 or apoE? (apolipoprotein adj E))	85	L2

L1	Zannis-Vassilis-I$.in.	3	L1

END OF SEARCH HISTORY

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Date: 9/10/2005

Time: 12:47:39

Inventor Name Search

Enter the **first few letters** of the Inventor's Last Name.
Additionally, enter the **first few letters** of the Inventor's First name.

Last Name	First Name	
Zannis	Vassilis	Search

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Q3, 2005

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            $0.80    0.228 DialUnits File1
     $0.80  Estimated cost File1
     $0.03  INTERNET
     $0.83  Estimated cost this search
     $0.83  Estimated total session cost   0.228 DialUnits

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        (c) format only 2005 Dialog
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S (TRUNCATED OR VARIANT OR FRAGMENT OR DELETED) (S) (APOE OR APOE? OR (APOLIPOPROTEI
          196147  TRUNCATED
          186043  VARIANT
          337228  FRAGMENT
           56166  DELETED
           16688  APOE
           23064  APOE?
           79751  APOLIPOPROTEIN
         1960930  E
           25305  APOLIPOPROTEIN(W)E
      S1    1855  (TRUNCATED OR VARIANT OR FRAGMENT OR DELETED) (S) (APOE
                  OR APOE? OR (APOLIPOPROTEIN (W) E))
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S S1 AND (HYPERLIPIDEMIA OR CHOLESTEROL OR HYPERTRIGLYCERIDEMIA)
            1855  S1
           56201  HYPERLIPIDEMIA
          409264  CHOLESTEROL
           19454  HYPERTRIGLYCERIDEMIA
      S2     569  S1 AND (HYPERLIPIDEMIA OR CHOLESTEROL OR
                  HYPERTRIGLYCERIDEMIA)
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S S2 AND (VECTOR OR ADENOVIRUS OR ADENOVIRAL OR PLASMID)
             569  S2
          292910  VECTOR
           77223  ADENOVIRUS
           19100  ADENOVIRAL
          198789  PLASMID
      S3      39  S2 AND (VECTOR OR ADENOVIRUS OR ADENOVIRAL OR PLASMID)
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S S4 NOT PY>2001
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         5716239  PY>2001
      S5      17  S4 NOT PY>2001
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  5/3,K/1     (Item 1 from file: 155)
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13776319 PMID: 11439103
Identification of a peroxisome-proliferator-activated-receptor response element in the apolipoprotein E gene control region.
Galetto R; Albajar M; Polanco J I; Zakin M M; Rodriguez-Rey J C
Departamento de Biologia Molecular, Unidad Asociada al Centro de Investigaciones Biologicas, Universidad de Cantabria, Avda Cardenal Herrera Oria s/n, 39011 Santander, Spain.
Biochemical journal (England) Jul 15 2001, 357 (Pt 2) p521-7, ISSN 0264-6021 Journal Code: 2984726R
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Apolipoprotein E (**apoE**) is a protein involved in reverse **cholesterol** transport. Among other tissues, **apoE** is expressed in macrophages where its expression increases when macrophages develop into foam cells. It has been recently shown that peroxisome-proliferator-activated receptor gamma (PPARgamma) is involved in this conversion. Northern-blot analysis was carried out in the macrophage cell line THP1 to determine whether **apoE** mRNA levels were regulated by ciglitazone, a PPARgamma inducer. The results indicated that treatment with ciglitazone doubled the levels of **apoE** mRNA. To identify a possible PPARgamma response element (PPRE), several portions of **apoE** gene control region were used to construct luciferase reporter plasmids. In U-87 MG cells, a 185 bp **fragment** located in the **apoE** /apoCI intergenic region was sufficient to induce a 10-fold increase in the luciferase activity of the extract of cells co-transfected with a PPARgamma expression **plasmid** . Subsequent analysis revealed the presence of a sequence with a high level of sequence similarity to the consensus PPRE. Mutations in this sequence resulted in a lack of functionality both in transient transfection and in electrophoretic-mobility-shift assays. These results demonstrated the presence of a functional PPRE in the **apoE** /apoCI intergenic region. These results have implications for the regulation of **apoE** gene expression and could be relevant for understanding the anti-atherogenic effect of thiazolidinediones.

5/3,K/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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13732366 PMID: 11279066
Domains of apolipoprotein E contributing to triglyceride and cholesterol **homeostasis in vivo. Carboxyl-terminal region 203-299 promotes hepatic very low density lipoprotein-triglyceride secretion.**
Kypreos K E; van Dijk K W; van Der Zee A; Havekes L M; Zannis V I
Whitaker Cardiovascular Institute, Department of Medicine, Boston University School of Medicine, Boston, Massachusetts 02118, USA.
Journal of biological chemistry (United States) Jun 8 2001, 276 (23) p19778-86, ISSN 0021-9258 Journal Code: 2985121R
Contract/Grant No.: AG12717; AG; NIA
Publishing Model Print-Electronic
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Domains of apolipoprotein E contributing to triglyceride and cholesterol **homeostasis in vivo. Carboxyl-terminal region 203-299 promotes hepatic**

very low density lipoprotein-triglyceride secretion.
Apolipoprotein (apo) E has been implicated in **cholesterol** and triglyceride homeostasis in humans. At physiological concentration **apoE** promotes efficient clearance of **apoE** -containing lipoprotein remnants. However, high **apoE** plasma levels correlate with high plasma triglyceride levels. We have used **adenovirus** -mediated gene transfer in **apoE** -deficient mice (E(-)/-) to define the domains of **apoE** required for **cholesterol** and triglyceride homeostasis in vivo. A dose of 2 x 10(9) plaque-forming units of **apoE4** -expressing **adenovirus** reduced slightly the **cholesterol** levels of E(-)/- mice and resulted in severe **hypertriglyceridemia** , due to accumulation of **cholesterol** and triglyceride-rich very low density lipoprotein particles in plasma. In contrast, the **truncated** form **apoE4** -202 resulted in a 90% reduction in the plasma **cholesterol** levels but did not alter plasma triglyceride levels in the E(-)/- mice. **ApoE** secretion by cell cultures, as well as the steady-state hepatic mRNA levels in individual mice expressing **apoE4** or **apoE4** -202, were similar. In contrast, very low density lipoprotein-triglyceride secretion in mice expressing **apoE4** , but not **apoE4** -202, was increased 10-fold, as compared with mice infected with a control **adenovirus** . The findings suggest that the amino-terminal 1-202 region of **apoE4** contains the domains required for the in vivo clearance of lipoprotein remnants. Furthermore, the carboxyl-terminal 203-299 residues of **apoE** promote hepatic very low density lipoprotein-triglyceride secretion and contribute to **apoE** -induced **hypertriglyceridemia** .
Descriptors: *Apolipoproteins E--metabolism--ME; * **Cholesterol** --metabolism--ME; *Homeostasis; *Triglycerides--metabolism--ME; Adenoviridae--genetics--GE; Animals; Apolipoproteins E--blood--BL; Apolipoproteins E--chemistry--CH; Apolipoproteins E--genetics--GE; Base Sequence; **Cholesterol** --blood--BL; Chromatography, Liquid; DNA Primers; Humans; Liver--metabolism--ME; Mice; Mice, Knockout; RNA, Messenger--genetics--GE; RNA, Messenger--metabolism--ME; Triglycerides--blood--BL; Tumor...
Chemical Name: Apolipoproteins E; DNA Primers; RNA, Messenger; Triglycerides; apolipoprotein E-4; **Cholesterol**

5/3,K/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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13705748 PMID: 11352738
The amino-terminal 1-185 domain of apoE promotes the clearance of lipoprotein remnants in vivo. The carboxy-terminal domain is required for induction of hyperlipidemia **in normal and apoE-deficient mice.**
Kypreos K E; Morani P; van Dijk K W; Havekes L M; Zannis V I
Whitaker Cardiovascular Institute, Department of Medicine, Boston University School of Medicine, Boston, Massachusetts 02118-2394, USA.
Biochemistry (United States) May 22 2001, 40 (20) p6027-35, ISSN 0006-2960 Journal Code: 0370623
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

The amino-terminal 1-185 domain of apoE promotes the clearance of lipoprotein remnants in vivo. The carboxy-terminal domain is required for induction of hyperlipidemia **in normal and apoE-deficient mice.**
Apolipoprotein E (**apoE**) promotes receptor-mediated catabolism of **apoE** -containing lipoprotein remnants. Impairments in remnant clearance are

associated with type III hyperlipoproteinemia and premature atherosclerosis. In humans, **apoE** plasma levels correlate with plasma triglyceride levels, suggesting that excess **apoE** may also affect plasma triglyceride levels. We have used **adenovirus** -mediated gene transfer in mice to map the domains of **apoE** required for **cholesterol** and triglyceride clearance, in vivo. **Adenovirus** expressing **apoE3** and□apoE4□ at doses of (1-2) x 10(9) pfu increased plasma **cholesterol** and triglyceride levels in normal C57BL6 mice and failed to normalize the high **cholesterol** levels of **apoE** -deficient mice due to induction of **hypertriglyceridemia** . In contrast, an **adenovirus** expressing the **truncated** **apoE** 1-185 form normalized the **cholesterol** levels of E(-)(/)(-) mice and did not cause **hypertriglyceridemia** . Northern blot analysis of hepatic RNA from mice expressing the full-length and the **truncated** **apoE** forms showed comparable steady-state **apoE** mRNA levels of the full-length **apoE** forms that cause **hyperlipidemia** and the **truncated** **apoE** forms that do not cause **hyperlipidemia** . The findings suggest that the amino-terminal residues 1-185 of **apoE** are sufficient for the clearance of **apoE** -containing lipoprotein remnants by the liver, whereas domains of the carboxy-terminal one-third of **apoE** are required for **apoE** -induced **hyperlipidemia** .

Descriptors: *Apolipoproteins E--physiology--PH; * **Hyperlipidemia** --genetics--GE; *Lipoproteins--metabolism--ME; *Peptide Fragments --physiology--PH...; GE; Chromatography, High Pressure Liquid; Gene Deletion; Genetic Vectors--chemistry--CH; Genetic Vectors--metabolism--ME; Humans; Hypercholesterolemia--blood--BL; Hypercholesterolemia--etiology --ET; Hypercholesterolemia--genetics--GE; **Hyperlipidemia** --blood--BL; **Hyperlipidemia** --etiology--ET; **Hypertriglyceridemia** --blood--BL; **Hypertriglyceridemia** --etiology--ET; **Hypertriglyceridemia** --genetics--GE ; Lipoproteins--blood--BL; Lipoproteins, VLDL--secretion--SE; Liver --secretion--SE; Mice; Mice, Inbred C57BL; Mice, Knockout; Peptide Fragments--genetics--GE; Protein Structure, Tertiary...

5/3,K/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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12946455 PMID: 10894820

Apolipoprotein E2 (Lys146-->Gln) causes hypertriglyceridemia **due to an apolipoprotein E** variant **-specific inhibition of lipolysis of very low density lipoproteins-triglycerides.**

de Beer F; van Dijk K W; Jong M C; van Vark L C; van der Zee A; Hofker M H; Fallaux F J; Hoeben R C; Smelt A H; Havekes L M

TNO-Prevention and Health, Gaubius Laboratory, Leiden, the Netherlands.

Arteriosclerosis, thrombosis, and vascular biology (UNITED STATES) Jul 2000, 20 (7) p1800-6, ISSN 1079-5642 Journal Code: 9505803

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Apolipoprotein E2 (Lys146-->Gln) causes hypertriglyceridemia **due to an apolipoprotein E** variant **-specific inhibition of lipolysis of very low density lipoproteins-triglycerides.**

...apolipoprotein E2 (Lys146-->Gln) variant is associated with a dominant form of familial dysbetalipoproteinemia. Heterozygous carriers of this variant have elevated levels of plasma triglycerides, **cholesterol** , and **apolipoprotein E (apoE)**. It was hypothesized that the high amounts of triglycerides in the very low density lipoprotein (VLDL) fraction are due

to a disturbed lipolysis of VLDL. To test this hypothesis, **apoE** knockout mice were injected with an **adenovirus** containing the human **APOE** *2 (Lys146-->Gln) gene, Ad-E2(146), under the control of the cytomegalovirus promoter. **ApoE** knockout mice injected with an **adenovirus vector** encoding human **apoE3** (Ad-E3) were used as controls. Five days after **adenovirus** injection, plasma **cholesterol** levels of mice injected with a high dose of Ad-E2(146) (2x10(9) plaque-forming units) were not changed compared with preinjection levels, whereas...

... of Ad-E2(146) (5x10(8) plaque-forming units) and in the groups injected with a low or a high dose of Ad-E3, plasma **cholesterol** levels were decreased 5-, 6-, and 12-fold, respectively. Plasma triglycerides were not affected in mice injected with Ad-E3. In contrast, a 7-fold...

... of plasma triglycerides (50-fold compared with Ad-E3 injection). In vitro lipolysis experiments showed that the lipolysis rate of VLDLs containing normal amounts of **apoE2** (Lys146-->Gln) was decreased by 54% compared with that of VLDLs containing comparable amounts of **apoE3** . The in vivo VLDL-triglyceride production rate of Ad-E2(146)-injected mice was not significantly different from that of Ad-E3-injected mice. These results demonstrate that expression of **apoE2** (Lys146-->Gln) causes **hypertriglyceridemia** due to an **apoE variant** -specific inhibition of the hydrolysis of VLDL-triglycerides.

Descriptors: *Apolipoproteins E--genetics--GE; * **Hypertriglyceridemia** --genetics--GE; *Lipoproteins, VLDL--metabolism--ME; *Point Mutation; *Triglycerides--metabolism--ME...; Alleles; Animals; Apolipoproteins E --blood--BL; Gene Expression--physiology--PH; Gene Transfer Techniques; Humans; Hydrolysis; Hyperlipoproteinemia Type III--genetics--GE; Hyperlipoproteinemia Type III--metabolism--ME; **Hypertriglyceridemia** --metabolism--ME; Lipolysis--genetics--GE; Liver--metabolism--ME; Mice; Mice, Knockout; RNA, Messenger--analysis--AN

5/3,K/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2005 Dialog. All rts. reserv.

12276964 PMID: 9588907
Reduction in amyloid A amyloid formation in apolipoprotein-E-deficient mice.
Kindy M S; Rader D J
Department of Biochemistry, University of Kentucky School of Medicine, and the Veterans Affairs Medical Center, Lexington 40536-0084, USA. mskindy@pop.uky.edu
American journal of pathology (UNITED STATES) May 1998, 152 (5) p1387-95, ISSN 0002-9440 Journal Code: 0370502
Contract/Grant No.: AG-12860; AG; NIA; NS-31220; NS; NINDS
Publishing Model Print; Comment in Am J Pathol. 1998 May;152(5) 1125-7; Comment in PMID 9588878
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Apolipoproteins have been implicated in the formation of amyloid fibrils. Recent studies have demonstrated that apolipoprotein E (**apoE**), alone or in combination with apolipoprotein J (apoJ), and other lipoproteins appear to enhance deposition of amyloid fibrils both in systemic and cerebral amyloids, especially Alzheimer's disease (AD). **ApoE** enhanced the ability of the amyloid beta-protein (1-40) **fragment** (A beta) to form fibrils in

vitro, with **apoE4** promoting the greatest fibril formation. **ApoE** was found associated with both human and mouse amyloid A (AA) deposits. To define the role of **apoE** in vivo, we utilized mice lacking the **apoE** gene by gene targeting. We used the AA model in mice to characterize the function of the **apoE** protein in amyloid fibrillogenesis. **ApoE** -deficient mice exhibited a decrease in deposition of AA when compared with heterozygous mutant or wild-type animals. In addition, **apoE** -deficient mice that were injected with an **adenovirus** that expressed the human **apoE3** gene had restored AA deposition and the **apoE** was associated with the AA fibrils. These results are agreement with the in vitro studies using the beta-peptide and suggest that **apoE** is not essential for amyloid fibrillogenesis but can promote the development of amyloid deposition.
...; genetics--GE; Amyloidosis--blood--BL; Amyloidosis--metabolism--ME; Animals; Apolipoproteins E--genetics--GE; Blotting, Southern; Disease Models, Animal; Glycoproteins--administration and dosage--AD; Lipoproteins, HDL **Cholesterol** --blood--BL; Mice; Mice, Inbred C57BL; Mice, Knockout; Nucleic Acids--chemistry--CH; Polymerase Chain Reaction; Silver Nitrate --administration and dosage--AD; Spleen--metabolism--ME; Triglycerides...
Chemical Name: Acute-Phase Proteins; Apolipoproteins E; Glycoproteins; Lipoproteins, HDL **Cholesterol** ; Nucleic Acids; Serum Amyloid A Protein; Triglycerides; amyloid enhancing factor; apolipoprotein E-3; Silver Nitrate

5/3,K/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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11627877 PMID: 8940032
In the absence of endogenous mouse apolipoprotein E, apolipoprotein E*2(Arg-158 --> Cys) transgenic mice develop more severe hyperlipoproteinemia than apolipoprotein E*3-Leiden transgenic mice.
van Vlijmen B J; van Dijk K W; van't Hof H B; van Gorp P J; van der Zee A ; van der Boom H; Breuer M L; Hofker M H; Havekes L M
TNO Prevention and Health, Gaubius Laboratory, 2301 CE Leiden, The Netherlands. lm.havekes@pg.tno.nl
Journal of biological chemistry (UNITED STATES) Nov 29 1996, 271 (48) p30595-602, ISSN 0021-9258 Journal Code: 2985121R
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Apolipoprotein E*2(Arg-158 --> Cys) (APOE*2) transgenic mice were generated and compared to the previously generated apolipoprotein E*3-Leiden (**APOE** *3-Leiden) transgenic mice to study the variable expression of hyperlipoproteinemia associated with these two **APOE** variants. In the presence of the endogenous mouse **Apoe** gene, the expression of the **APOE** *3-Leiden gene resulted in slightly elevated levels of serum **cholesterol** as compared with control mice (2.7 +/- 0. 5 versus 2.1 +/- 0.2 mmol/liter, respectively), whereas the expression of the **APOE** *2(Arg-158 --> Cys) gene did not affect serum **cholesterol** levels, even after high/fat **cholesterol** feeding. The extreme **cholesterol** level usually found in **apoE** -deficient mice (**Apoe** -/- mice; 23.6 +/- 5.0 mmol/liter) could be rescued by introducing the **APOE** *3-Leiden gene (**APOE** *3-Leiden. **Apoe** -/-; 3.6 +/- 1. 5 mmol/liter), whereas the expression of the **APOE** *2(Arg-158 --> Cys) gene in **Apoe** -/- mice minimally reduced serum **cholesterol** levels (**APOE** *2.□Apoe□ -/-; 16.6 +/- 2.9 mmol/liter). In vivo very low density lipoprotein (VLDL) turnover studies revealed that **APOE** *2. **Apoe** -/- VLDL and□APOE□ *3-Leiden.□Apoe□ -/- VLDL display strongly

reduced fractional catabolic rates as compared with control mouse VLDL (4.0 and 6.1 versus 22.1 pools/h). In vitro low density lipoprotein (LDL) receptor binding studies using HepG2 and J774 cells showed that **APOE** *2. **Apoe** -/- VLDL is completely defective in binding to the LDL receptor, whereas **APOE** *3-Leiden. **Apoe** -/- VLDL still displayed a considerable binding activity to the LDL receptor. After transfection of **APOE** *2. **Apoe** -/- and **APOE** *3-Leiden. **Apoe** -/- mice with□adenovirus□carrying the gene for the receptor-associated protein (AdCMV-RAP), serum lipid levels strongly increased (15.3 to 42.8 and 1.4 to 15.3 mmol/liter for **cholesterol** and 5.0 to 35.7 and 0.3 to 20. 7 mmol/liter for triglycerides, respectively). This indicates that RAP-sensitive receptors, possibly the LDL receptor-related protein (LRP), mediate the plasma clearance of both **APOE** *2. **Apoe** -/- and□APOE□ *3-Leiden.□Apoe□ -/-. VLDL. We conclude that in vivo the **APOE** *2 **variant** is completely defective in LDL receptor binding but not in binding to LRP, whereas for the **APOE** *3-Leiden mutant both LRP and LDL receptor binding activity are only mildly affected. As a consequence of this difference, **APOE** *2. **Apoe** -/- develop more severe hypercholesterolemia than **APOE** *3-Leiden **Apoe** -/- mice.

5/3,K/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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11583971 PMID: 8895066
Hepatic gene transfer of the catalytic subunit of the apolipoprotein B mRNA editing enzyme results in a reduction of plasma LDL levels in normal and watanabe heritable hyperlipidemic rabbits.
Greeve J; Jona V K; Chowdhury N R; Horwitz M S; Chowdhury J R
Medizinische Klinik, Universitats-Krankenhaus Eppendorf, Hamburg, Germany.
Journal of lipid research (UNITED STATES) Sep 1996, 37 (9) p2001-17, ISSN 0022-2275 Journal Code: 0376606
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

... liver of rabbits reconstitutes hepatic apoB mRNA editing and how this affects the plasma levels of apoB-containing lipoproteins, we constructed an APOBEC-1 recombinant **adenovirus** (Ad APOBEC-1). After injection of Ad APOBEC-1 into normal New Zealand White (NZW) or Watanabe heritable hyperlipidemic (WHHL) rabbits, up to 50% of...
... APOBEC-1-treated NZW and WHHL rabbits contained both apoB-100 and apoB-48, whereas that from control rabbits infected with a beta-galactosidase recombinant **adenovirus** (Ad LacZ) contained exclusively apoB-100. VLDL from WHHL rabbits treated with Ad APOBEC-1 had the same particle size, lipid composition, and content of **apolipoprotein E** as VLDL from Ad LacZ-infected control animals. An increase of VLDL was observed in NZW and WHHL rabbits after infection with Ad APOBEC-1...
Descriptors: *Cytidine Deaminase--genetics--GE; *Gene Transfer Techniques ; * **Hyperlipidemia** --metabolism--ME; *Lipoproteins, LDL--blood--BL; *Liver --metabolism--ME; *RNA Editing; Adenoviridae--genetics--GE; Animals; Apolipoproteins B--metabolism--ME; Fasting; **Hyperlipidemia** --genetics--GE; Lipoproteins, HDL **Cholesterol** --blood--BL; Lipoproteins, LDL--chemistry --CH; Lipoproteins, LDL **Cholesterol** --blood--BL; Lipoproteins, VLDL --chemistry--CH; Lipoproteins, VLDL--ultrastructure--UL; Lipoproteins, VLDL **Cholesterol** --blood--BL; Rabbits; Rats; Triglycerides--blood--BL
Chemical Name: Apolipoproteins B; Lipoproteins, HDL **Cholesterol** ;

Lipoproteins, LDL; Lipoproteins, LDL **Cholesterol** ; Lipoproteins, VLDL; Lipoproteins, VLDL **Cholesterol** ; Triglycerides; apolipoprotein B-100; AICDA (activation-induced cytidine deaminase); Cytidine Deaminase; apolipoprotein B mRNA editing enzyme

5/3,K/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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10787736 PMID: 7989859
Expression of heterologous human apolipoprotein E by J774 macrophages enhances cholesterol **efflux to HDL3.**
Mazzone T; Reardon C
Department of Medicine, Rush Medical College, Chicago, IL 60612.
Journal of lipid research (UNITED STATES) Aug 1994, 35 (8) p1345-53, ISSN 0022-2275 Journal Code: 0376606
Contract/Grant No.: HL15062; HL; NHLBI; HL39653; HL; NHLBI
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Expression of heterologous human apolipoprotein E by J774 macrophages enhances cholesterol **efflux to HDL3.**
Expression of apolipoprotein (apo) E by macrophages is tightly regulated by cellular **cholesterol** content. We have investigated a potential modulating role for **apoE** on macrophage **cholesterol** homeostasis by stably transfecting the J774 macrophage, which does not express its endogenous **apoE** gene, with a human **apoE** cDNA expression□vector□and comparing **cholesterol** homeostasis in this cell line with that of a control line transfected with the neomycin resistance construct only. Incubation in serum-free medium after **cholesterol** loading produced no difference in cellular **cholesterol** content between **apoE** secreting and non-secreting J774 cells. Similarly, in serum-free medium there was no difference in the amount of radiolabeled **cholesterol** effluxed. Addition of cAMP or S58035 to **cholesterol** -loaded J774 cells did enhance efflux of radiolabeled **cholesterol** from **apoE** secreting compared to non-secreting macrophages but did not detectably alter cellular free **cholesterol** or cholesteryl ester mass. Incubation with HDL3 alone, however, significantly decreased macrophage cholesteryl ester mass compared to a 24-h incubation in serum-free medium from 10.5 +/- 3.9 to 3.2 +/- 2.0 ($P < 0.01$) in **apoE** -secreting J774 cells. During a 24-h incubation in HDL3, cholesteryl ester fell from 6.4 +/- 2.4 to 0.8 +/- 0.7 (delta = 5.6 micrograms/mg) in **apoE** -secreting cells and from 9.3 +/- 2.2 to 7.7 +/- micrograms/mg (delta = 1.6 micrograms/mg) in non-secreting cells ($P < 0.005$ **apoE** -secreting vs. non-secreting cells).(ABSTRACT **TRUNCATED** AT 250 WORDS)
Descriptors: *Apolipoproteins E--secretion--SE; * **Cholesterol** --metabolism--ME; *Lipoproteins, HDL--pharmacology--PD; *Macrophages --metabolism--ME; Apolipoproteins E--genetics--GE; Cell Line; **Cholesterol** --pharmacology--PD; **Cholesterol** Esters--metabolism--ME; DNA, Complementary; Gene Transfer Techniques; Humans; Macrophages--drug effects --DE
Chemical Name: Apolipoproteins E; **Cholesterol** Esters; DNA, Complementary; Lipoproteins, HDL; **Cholesterol**

5/3,K/9 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

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0013670079 BIOSIS NO.: 200200263590
Liver-specific overexpression of a ligand-independent ERalpha- variant **induces hypolipidemia in male** APOE3Leiden **mice: Using genomic technology to identify potential pathways of estrogen action in the liver**
AUTHOR: d'Oliveira Christine (Reprint); van der Zee Andre (Reprint); Mank Eveline (Reprint); Boer Judith M (Reprint); den Dunnen Johan T (Reprint); Frants Rune R (Reprint); Havekes Louis M; Katzenellenbogen Benita S; van Dijk Ko Willems
AUTHOR ADDRESS: Leiden Univ Med Ctr, Leiden, Netherlands**Netherlands
JOURNAL: Circulation 104 (17 Supplement): pII.115 October 23, 2001 2001
MEDIUM: print
CONFERENCE/MEETING: Scientific Sessions 2001 of the American Heart Association Anaheim, California, USA November 11-14, 2001; 20011111
SPONSOR: American Heart Association
ISSN: 0009-7322
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

Liver-specific overexpression of a ligand-independent ERalpha- variant **induces hypolipidemia in male** APOE3Leiden **mice: Using genomic technology to identify potential pathways of estrogen action in the liver**
...REGISTRY NUMBERS: **cholesterol**
DESCRIPTORS:
ORGANISMS: **adenovirus** (Adenoviridae...

...gene **vector** ;
CHEMICALS & BIOCHEMICALS: ... **cholesterol** --

5/3,K/10 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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0013670077 BIOSIS NO.: 200200263588
Hyperlipidemia **in** APOE2 **transgenic mice is aggravated by overexpression of full length** APOE3 **whereas it is reduced by a** truncated ApoE variant
AUTHOR: Gerritsen Gery (Reprint); Kypreos Kyriakos E; van der Zee Andre; Zannis Vassilis I; Havekes Louis M; van Dijk Ko Willems
AUTHOR ADDRESS: Leiden Univ Med Ctr, Leiden, Netherlands**Netherlands
JOURNAL: Circulation 104 (17 Supplement): pII.114-II.115 October 23, 2001 2001
MEDIUM: print
CONFERENCE/MEETING: Scientific Sessions 2001 of the American Heart Association Anaheim, California, USA November 11-14, 2001; 20011111
SPONSOR: American Heart Association
ISSN: 0009-7322
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

Hyperlipidemia **in** APOE2 **transgenic mice is aggravated by overexpression of full length** APOE3 **whereas it is reduced by a** truncated ApoE variant
...REGISTRY NUMBERS: **cholesterol**
DESCRIPTORS:
ORGANISMS: **adenovirus** (Adenoviridae...

...gene **vector** ;
...DISEASES: **hyperlipidemia** --
MESH TERMS: **Hyperlipidemia** (MeSH)
CHEMICALS & BIOCHEMICALS: ... **cholesterol** --

5/3,K/11 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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0012684462 BIOSIS NO.: 200000402775
Apolipoprotein E2 (Lys146fwdarwGln) causes hypertriglyceridemia **due to an apolipoprotein E** variant **-specific inhibition of lipolysis of very low density lipoproteins-triglycerides**
AUTHOR: de Beer Femke; van Dijk Ko Willems; Jong Miek C; van Vark Leonie C; van der Zee Andre; Hofker Marten H; Fallaux Frits J; Hoeben Rob C; Smelt Augustinus H M; Havekes Louis M (Reprint)
AUTHOR ADDRESS: Gaubius Laboratory, TNO-Prevention and Health, Zernikedreef 9, 2333 CK, Leiden, Netherlands**Netherlands
JOURNAL: Arteriosclerosis Thrombosis and Vascular Biology 20 (7): p 1800-1806 July, 2000 2000
MEDIUM: print
ISSN: 1079-5642
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

Apolipoprotein E2 (Lys146fwdarwGln) causes hypertriglyceridemia **due to an apolipoprotein E** variant **-specific inhibition of lipolysis of very low density lipoproteins-triglycerides**
ABSTRACT: The apolipoprotein E2 (Lys146fwdarwGln) variant is associated with a dominant form of familial dysbetalipoproteinemia. Heterozygous carriers of this variant have elevated levels of plasma triglycerides, **cholesterol** , and **apolipoprotein E** (□apoE□). It was hypothesized that the high amounts of triglycerides in the very low density lipoprotein (VLDL) fraction are due to a disturbed lipolysis of VLDL. To test this hypothesis, **apoE** knockout mice were injected with an **adenovirus** containing the human **APOE** *2 (Lys146fwdarwGln) gene, Ad-E2(146), under the control of the cytomegalovirus promoter. **ApoE** knockout mice injected with an **adenovirus** **vector** encoding human **apoE3** (Ad-E3) were used as controls. Five days after **adenovirus** injection, plasma **cholesterol** levels of mice injected with a high dose of Ad-E2(146) (2X109 plaque-forming units) were not changed compared with preinjection levels, whereas in...

...dose of Ad-E2(146) (5X108 plaque-forming units) and in the groups injected with a low or a high dose of Ad-E3, plasma **cholesterol** levels were decreased 5-, 6-, and 12-fold, respectively. Plasma triglycerides were not affected in mice injected with Ad-E3. In contrast, a 7-fold...

...of plasma triglycerides (50-fold compared with Ad-E3 injection). In vitro lipolysis experiments showed that the lipolysis rate of VLDLs containing normal amounts of **apoE2** (Lys146fwdarwGln) was decreased by 54% compared with that of VLDLs containing comparable amounts of **apoE3** . The in vivo VLDL-triglyceride production rate of Ad-E2(146)-injected mice was not significantly different from that of Ad-E3-injected mice. These results demonstrate that expression of **apoE2** (Lys146fwdarwGln) causes **hypertriglyceridemia** due to an **apoE** **variant** -specific inhibition of the hydrolysis of VLDL-triglycerides.

DESCRIPTORS:
ORGANISMS: **adenovirus** (Adenoviridae...

...gene **vector** ;
...DISEASES: **hypertriglyceridemia** --
MESH TERMS: **Hypertriglyceridemia** (MeSH)
METHODS & EQUIPMENT: **adenovirus** -mediated gene transfer...
MISCELLANEOUS TERMS: ...apolipoprotein E **variant** -specific inhibition

5/3,K/12 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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0012596262 BIOSIS NO.: 200000314575
Sterols and inhibitors of sterol transport modulate the degradation and secretion of macrophage apoE: Requirement for the C-terminal domain
AUTHOR: Duan Hongwei; Gu Desheng; Mazzone Theodore (Reprint)
AUTHOR ADDRESS: Department of Medicine, Rush Medical College, 1653 W. Congress Parkway, Chicago, IL, 60612, USA**USA
JOURNAL: Biochimica et Biophysica Acta 1484 (2-3): p142-150 April 12, 2000 2000
MEDIUM: print
ISSN: 0006-3002
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Macrophage-derived **apoE** , produced in the vessel wall, may have important effects during atherogenesis. The production of **apoE** by macrophages can be regulated at a transcriptional level by cellular differentiation state, cytokines and sterol loading. In addition, there are post-transcriptional and post-translational loci for regulation. We have recently identified an intermediate density cell membrane fraction in which the degradation of **apoE** can be modulated by sterols. Suppressing degradation of **apoE** in this fraction by pre-incubating cells in sterols led to enhanced **apoE** secretion. In this report we demonstrate that the suppressive effect of sterols on the degradation of newly synthesized **apoE** in this fraction depends on the presence on its C-terminal domain, by studying a macrophage cell line transfected to express a mutant form of **apoE** in which amino acids beyond amino acid 202 were **deleted** . In addition, two modulators of cellular sterol transport, progesterone and U1866A, inhibited the degradation of full-length **apoE** . In contrast, incubation of cells in the acyl-CoA: **cholesterol** acyltransferase inhibitor S58035 did not influence **apoE** degradation. As would be predicted based on the results of degradation assays, U1866A, but not S58035, increased the secretion of **apoE** from a cell line transfected to constitutively express full-length **apoE** cDNA. The effect of U1866A on **apoE** degradation, like the effect of sterol, required the presence of the **apoE** C-terminal domain. Our results indicate that alteration of intracellular sterol homeostasis by preincubation in sterols or by drugs that modify the subcellular transport of sterol, modulates the susceptibility of **apoE** to degradation and that this modulation requires the presence of C-terminal lipid binding domains.
DESCRIPTORS:
...METHODS & EQUIPMENT: gene expression/ **vector** techniques, molecular genetic method

5/3,K/13 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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0010684228 BIOSIS NO.: 199799318288
In the absence of endogenous mouse apolipoprotein E, apolipoprotein E*2(Arg-158 fwdarw Cys) transgenic mice develop more severe hyperlipoproteinemia than apolipoprotein E*3 Leiden transgenic mice
AUTHOR: Van Vlijmen Bart J M; Willems Van Dijk Ko; Van't Hof H Belinda; Van Gorp Patrick J J; Van Der Zee Andre; Van Der Boom Hans; Breuer Marco L; Hofker Martin H; Havekes Louis M (Reprint)
AUTHOR ADDRESS: TNO-PG, Gaubius Lab., PO Box 2215, 2301 CE Leiden, Netherlands**Netherlands
JOURNAL: Journal of Biological Chemistry 271 (48): p30595-30602 1996 1996
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Apolipoprotein E*2(Arg-158 fwdarw Cys) (APOE*2) transgenic mice were generated and compared to the previously generated apolipoprotein E*3-Leiden (**APOE** *3-Leiden) transgenic mice to study the variable expression of hyperlipoproteinemia associated with these two **APOE** variants. In the presence of the endogenous mouse **Apoe** gene, the expression of the **APOE** *3-Leiden gene resulted in slightly elevated levels of serum **cholesterol** as compared with control mice (2.7 +- 0.5 versus 2.1 +- 0.2 mmol/liter, respectively), whereas the expression of the **APOE** *2(Arg-158 fwdarw Cys) gene did not affect serum **cholesterol** levels, even after high/fat **cholesterol** feeding. The extreme **cholesterol** level usually found in **apoE** -deficient mice (□Apoe□ -/- mice; 23.6 +- 5.0 mmol/liter) could be rescued by introducing the **APOE** *3-Leiden gene (**APOE** *3-Leiden- **Apoe** -/-; 3.6 +- 1.5 mmol/liter), whereas the expression of the **APOE** *2(Arg-158 fwdarw Cys) gene in **Apoe** -/- mice minimally reduced serum **cholesterol** levels (**APOE** *2 cntdot **Apoe** -/-; 16.6 +- 2.9 mmol/liter). In vivo very low density lipoprotein (VLDL) turnover studies revealed that **APOE** *2 cntdot **Apoe** -/- VLDL and **APOE** *3 cntdot Leiden cntdot **Apoe** -/- VLDL display strongly reduced fractional catabolic rates as compared with control mouse VLDL (4.0 and 6.1 versus 22.1 pools/h). In vitro low density lipoprotein (LDL) receptor binding studies using HepG2 and J774 cells showed that **APOE** *2- **Apoe** -/- VLDL is completely defective in binding to the LDL receptor, whereas **APOE** *3-Leiden cntdot **Apoe** -/- VLDL still displayed a considerable binding activity to the LDL receptor. After transfection of **APOE** *2 cntdot **Apoe** -/- and **APOE** *3-Leiden cntdot□Apoe□ -/- mice with **adenovirus** carrying the gene for the receptor-associated protein (AdCMV-RAP), serum lipid levels strongly increased (15.3 to 42.8 and 1.4 to 15.3 mmol/liter for **cholesterol** and 5.0 to 35.7 and 0.3 to 20.7 mmol/liter for triglycerides, respectively). This indicates that RAP-sensitive receptors, possibly the LDL receptor-related protein (LRP), mediate the plasma clearance of both **APOE** *2 cntdot **Apoe** -/- and□APOE□ *3-Leiden cntdot **Apoe** -/- VLDL. We conclude that in vivo the **APOE** *2 **variant** is completely defective in LDL receptor binding but not in binding to LRP, whereas for the **APOE** *3-Leiden mutant both LRP and LDL receptor binding activity are only mildly affected. As a consequence of this difference, **APOE** *2- **Apoe** -/- develop more severe hypercholesterolemia than **APOE** *3-Leiden cntdot **Apoe** -/- mice.
...REGISTRY NUMBERS: **CHOLESTEROL**
DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: ... **CHOLESTEROL**
MISCELLANEOUS TERMS: ... **CHOLESTEROL** ;

5/3,K/14 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE
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11413262 EMBASE No: 2001426442
Evaluation of the role of lipoprotein metabolism genes in systemic cationic liposome-mediated gene transfer In Vivo
Mounkes L.C.; Zhong W.; De Silva H.V.; Handumrongkul C.; Desai B.; Tse E.; Taylor J.M.; Debs R.J.
Dr. R.J. Debs, California Pac. Med. Ctr. Res. Inst., Stern Bldg., 2330 Clay St., San Francisco, CA 94115 United States
AUTHOR EMAIL: debs@cooper.cpmc.org
Human Gene Therapy (HUM. GENE THER.) (United States) 2001, 12/16 (1939-1954)
CODEN: HGTHE ISSN: 1043-0342
DOCUMENT TYPE: Journal ; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 42

...for, or overexpressing, selected genes involved in lipoprotein metabolism, for their potential to regulate intravenous, CLDC-based gene delivery. Although homozygous knockout mutation in the **apoE** gene caused a significant decrease in gene expression in many tissues of **apoE** -deficient mice, mice with homozygous deletion of both the **apoE** and LDLR genes showed wild-type levels of gene transfer efficiency. Thus, a secondary event, produced by homozygous deletion of **apoE** , but compensated for by the concomitant deletion of LDLR, and/or effects resulting from strain-related, genetic background differences, appeared to play a significant role...

...germ line knockouts, as well as epigenetic effects produced by strain differences, may limit the ability to assign specific, gene transfer-related functions to the **deleted** gene.
DRUG DESCRIPTORS:
*liposome--intravenous drug administration--iv; * **plasmid** DNA --pharmacology--pd; * **plasmid** DNA--intravenous drug administration--iv ...gene product--endogenous compound--ec; apolipoprotein E--endogenous compound--ec; apolipoprotein A1--endogenous compound--ec; high density lipoprotein--endogenous compound--ec; triacylglycerol--endogenous compound --ec; **cholesterol** --endogenous compound--ec
MEDICAL DESCRIPTORS:
gene overexpression; knockout mouse; transgenic mouse; genetic transfection; gene deletion; gene transfer; strain difference; experimental mouse; **cholesterol** blood level; lipoprotein blood level; triacylglycerol blood level; CHO cell; leukemia cell; drug mechanism; Cytomegalovirus; human; nonhuman; mouse; animal experiment; controlled study; human cell; animal...
CAS REGISTRY NO.: 2380-63-4 (4 aminopyrazolo[3,4 d]pyrimidine); 57-88-5 (**cholesterol**)

5/3,K/15 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE
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10779265 EMBASE No: 2000259350
Apolipoprotein E2 (Lys146<rt arrow>Gln) causes hypertriglyceridemia **due to an** apolipoprotein E variant **-specific inhibition of lipolysis of very low density lipoproteins-triglycerides**

De Beer F.; Van Dijk K.W.; Jong M.C.; Van Vark L.C.; Van der Zee A.; Hofker M.H.; Fallaux F.J.; Hoeben R.C.; Smelt A.H.M.; Havekes L.M.
Dr. L.M. Havekes, TNO-Prevention and Health, Gaubius Laboratory, Zernikedreef 9, 2333 CK Leiden Netherlands
AUTHOR EMAIL: LM.Havekes@PG.TNO.NL
Arteriosclerosis, Thrombosis, and Vascular Biology (ARTERIOSCLER. THROMB. VASC. BIOL.) (United States) 2000, 20/7 (1800-1806)
CODEN: ATVBF ISSN: 1079-5642
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 42

Apolipoprotein E2 (Lys146<rt arrow>Gln) causes hypertriglyceridemia **due to an** apolipoprotein E variant **-specific inhibition of lipolysis of very low density lipoproteins-triglycerides**

...Lys146<rt arrow>Gln) variant is associated with a dominant form of familial dysbetalipoproteinemia. Heterozygous carriers of this variant have elevated levels of plasma triglycerides, **cholesterol** , and **apolipoprotein E** (**apoE**). It was hypothesized that the high amounts of triglycerides in the very low density lipoprotein (VLDL) fraction are due to a disturbed lipolysis of VLDL. To test this hypothesis, **apoE** knockout mice were injected with an **adenovirus** containing the human **APOE** *2 (Lys146<rt arrow>Gln) gene, Ad-E2(146), under the control of the cytomegalovirus promoter. **ApoE** knockout mice injected with an **adenovirus vector** encoding human **apoE3** (Ad-E3) were used as controls. Five days after **adenovirus** injection, plasma **cholesterol** levels of mice injected with a high dose of Ad-E2(146) (2 x 10sup 9 plaque-forming units) were not changed compared with preinjection...

...E2(146) (5 x 10sup 8 plaque- forming units) and in the groups injected with a low or a high dose of Ad-E3, plasma **cholesterol** levels were decreased 5-, 6-, and 12-fold, respectively. Plasma triglycerides were not affected in mice injected with Ad-E3. In contrast, a 7-fold...

...of plasma triglycerides (50-fold compared with Ad-E3 injection). In vitro lipolysis experiments showed that the lipolysis rate of VLDLs containing normal amounts of **apoE2** (Lys146<rt arrow>Gln) was decreased by 54% compared with that of VLDLs containing comparable amounts of **apoE3** . The in vivo VLDL-triglyceride production rate of Ad-E2(146)-injected mice was not significantly different from that of Ad-E3-injected mice. These results demonstrate that expression of **apoE2** (Lys146<rt arrow>Gln) causes **hypertriglyceridemia** due to an **apoE variant** -specific inhibition of the hydrolysis of VLDL-triglycerides.
DRUG DESCRIPTORS:
apolipoprotein E3; isoprotein; **cholesterol** --endogenous compound--ec
MEDICAL DESCRIPTORS:
* **hypertriglyceridemia** --etiology--et; *lipolysis; *protein variant hyperlipoproteinemia type 3; triacylglycerol blood level; **cholesterol** blood level; lipoprotein blood level; promoter region; **Adenovirus** ; dose response; protein expression; hydrolysis; human; nonhuman; mouse; animal experiment; animal model; controlled study; animal tissue; article; priority journal
CAS REGISTRY NO.: 57-88-5 (**cholesterol**)

5/3,K/16 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE
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06703974 EMBASE No: 1996368923

In the absence of endogenous mouse apolipoprotein E, apolipoprotein E*2(Arg-158 <rt arrow> Cys) transgenic mice develop more severe hyperlipoproteinemia than apolipoprotein E*3-Leiden transgenic mice

Van Vlijmen B.J.M.; Van Dijk K.W.; Van't Hof H.B.; Van Gorp P.J.J.; Van der Zee A.; Van der Boom H.; Breuer M.L.; Hofker M.H.; Havekes L.M.
TNO-PG, Gaubius Laboratory, P. O. Box 2215,2301 CE Leiden Netherlands

Journal of Biological Chemistry (J. BIOL. CHEM.) (United States) 1996, 271/48 (30595-30602)
CODEN: JBCHA ISSN: 0021-9258
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Apolipoprotein E *2(Arg-155 <rt arrow> Cys) (**APOE** *2) transgenic mice were generated and compared to the previously generated **apolipoprotein E** *3- Leiden (**APOE** *3-Leiden) transgenic mice to study the variable expression of hyperlipoproteinemia associated with these two **APOE** variants. In the presence of the endogenous mouse **Apoe** gene, the expression of the **APOE** *3-Leiden gene resulted in slightly elevated levels of serum **cholesterol** as compared with control mice (2.7 +/- 0.5 versus 2.1 +/- 0.2 mmol/liter, respectively), whereas the expression of the **APOE** *2(Arg-158 <rt arrow> Cys) gene did not affect serum **cholesterol** levels, even after high/fat **cholesterol** feeding. The extreme **cholesterol** level usually found in **apoE** -deficient mice (**Apoe** (-/-) mice; 23.6 +/- 5.0 mmol/liter) could be rescued by introducing the **APOE** *3-Leiden gene (**APOE** *3-Leiden- **Apoe** (-/-); 3.6 +/- 1.5 mmol/liter), whereas the expression of the **APOE** *2(Arg-158 <rt arrow> Cys) gene in **Apoe** (-/-) mice minimally reduced serum **cholesterol** levels (**APOE** *2-□Apoe□ (-/-); 16.6 +/- 2.9 mmol/liter). In vivo very low density lipoprotein (VLDL) turnover studies revealed that **APOE** *2- **Apoe** (- /-) VLDL and□APOE□ *3-Leiden-□Apoe□ (-/-) VLDL display strongly reduced fractional catabolic rates as compared with control mouse VLDL (4.0 and 6.1 versus 22.1 pools/h). In vitro low density lipoprotein (LDL) receptor binding studies using HepG2 and J774 cells showed that **APOE** *2- **Apoe** (-/-) VLDL is completely defective in binding to the LDL receptor, whereas **APOE** *3- Leiden- **Apoe** (-/-) VLDL still displayed a considerable binding activity to the LDL receptor. After transfection of **APOE** *2- **Apoe** (-/-) and□APOE□ *3- Leiden-□Apoe□ (-/-) mice with□adenovirus□ carrying the gene for the receptor- associated protein (AdCMV-RAP), serum lipid levels strongly increased (15.3 to 42.8 and 1.4 to 15.3 mmol/liter for **cholesterol** and 5.0 to 35.7 and 0.3 to 20.7 mmol/liter for triglycerides, respectively). This indicates that RAP- sensitive receptors, possibly the LDL receptor-related protein (LRP), mediate the plasma clearance of both **APOE** *2- **Apoe** (-/-) and□APOE□ *3-Leiden-□Apoe□ (-/-) VLDL. We conclude that in vivo the **APOE** *2 **variant** is completely defective in LDL receptor binding but not in binding to LRP, whereas for the **APOE** *3- Leiden mutant both LRP and LDL receptor binding activity are only mildly affected. As a consequence of this difference, **APOE** *2- **Apoe** (-/-) develop more severe hypercholesterolemia than **APOE** *3-Leiden- **Apoe** (-/-) mice.

DRUG DESCRIPTORS:
cholesterol --endogenous compound--ec; complementary dna--endogenous compound--ec; lipid--endogenous compound--ec; low density lipoprotein receptor--endogenous compound--ec; messenger rna--endogenous compound--ec; receptor...

MEDICAL DESCRIPTORS:
animal cell; animal experiment; animal tissue; article; cell line; **cholesterol** blood level; **cholesterol** diet; controlled study; genetic transfection; lipid blood level; lipoprotein metabolism; metabolic rate; mouse; nonhuman; plasma clearance; priority journal; receptor binding; transgenic mouse

CAS REGISTRY NO.: 57-88-5 (**cholesterol**); 66455-18-3 (lipid)

5/3,K/17 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE
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06547890 EMBASE No: 1996208245
Transgenic mouse and gene therapy
Harada K.; Shimano H.; Ishibashi S.; Yamada N.
Third Dept. of Internal Medicine, Faculty of Medicine, Tokyo University, 7-3-1 Hongo,Bunkyo-ku, Tokyo 113 United States
Diabetes (DIABETES) (United States) 1996, 45/7 (S129-S132)
CODEN: DIAEA ISSN: 0012-1797
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

In the transgenic mouse, a specific gene can be transduced or **deleted** to study its function and relation to human diseases. Recently, various lines of transgenic mice that overexpress or lack a specific gene have been established and are available to study the pathophysiology of human diseases, including atherosclerosis, diabetes, and **hyperlipidemia** . We have established transgenic mouse fines with an integrated rat apolipoprotein (apo) E gene under control of the metallothionein promoter. Overexpression of **apoE** in the liver reduced plasma **cholesterol** and triglyceride levels and prevented diet- induced hypercholesterolemia. Another transgenic model with overexpression of **apoE** under control of the H2 Ld promoter in the arterial wall was established. In this model, the formation of fatty streak lesions was markedly inhibited, suggesting that **apoE** has antiatherogenic actions. Finally, we discuss gene therapy, which will be an important therapeutic approach to correct genetic abnormalities found in metabolic diseases.
MEDICAL DESCRIPTORS:
animal model; artery wall; atheroma; **cholesterol** blood level; **cholesterol** transport; conference paper; human; insulin release; insulin resistance; ischemic heart disease; liver; nonhuman; priority journal; transgenic mouse; triacylglycerol blood level; virus **vector**
?

```
Set     Items   Description
S1       1855   (TRUNCATED OR VARIANT OR FRAGMENT OR DELETED) (S) (APOE OR
           APOE? OR (APOLIPOPROTEIN (W) E))
S2        569   S1 AND (HYPERLIPIDEMIA OR CHOLESTEROL OR HYPERTRIGLYCERIDE-
           MIA)
S3         39   S2 AND (VECTOR OR ADENOVIRUS OR ADENOVIRAL OR PLASMID)
S4         23   RD (unique items)
S5         17   S4 NOT PY>2001
?

S S4 NOT S5
              23  S4
              17  S5
      S6       6  S4 NOT S5
?

T S6/3,K/ALL
```

6/3,K/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

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17610844 PMID: 15576362

Generation of a recombinant apolipoprotein E variant **with improved biological functions: hydrophobic residues (LEU-261, TRP-264, PHE-265, LEU-268, VAL-269) of** apoE **can account for the** apoE□-induced□ hypertriglyceridemia .

Kypreos Kyriakos E; van Dijk Ko W; Havekes Louis M; Zannis Vassilis I
Molecular Genetics, Department of Medicine, Boston University School of Medicine, Boston, Massachusetts 02118, USA.

Journal of biological chemistry (United States) Feb 25 2005, 280 (8) p6276-84, ISSN 0021-9258 Journal Code: 2985121R
Contract/Grant No.: HL68216; HL; NHLBI
Publishing Model Print-Electronic
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Generation of a recombinant apolipoprotein E variant **with improved biological functions: hydrophobic residues (LEU-261, TRP-264, PHE-265, LEU-268, VAL-269) of** apoE **can account for the** apoE□-induced□ hypertriglyceridemia .

To identify the residues in the carboxyl-terminal region 260-299 of human apolipoprotein E (apoE) that contribute to **hypertriglyceridemia** , two sets of conserved, hydrophobic amino acids between residues 261 and 283 were mutated to alanines, and recombinant adenoviruses expressing these apoE mutants were generated. **Adenovirus** -mediated gene transfer of apoE4-mut1 (apoE4 (L261A, W264A, F265A, L268A, V269A)) in apoE-deficient mice (apoE(-/-)) corrected plasma **cholesterol** levels and did not cause **hypertriglyceridemia** . In contrast, gene transfer of apoE4-mut2 (apoE4 (W276A, L279A, V280A, V283A)) did not correct hypercholesterolemia and induced mild **hypertriglyceridemia** . ApoE-induced **hyperlipidemia** was corrected by co-infection with a recombinant **adenovirus** expressing human lipoprotein lipase. Both apoE4 mutants caused only a small increase in hepatic very low density lipoprotein-triglyceride secretion. Density gradient ultracentrifugation analysis of...

...formation of spherical HDL. The findings indicate that residues Leu-261, Trp-264, Phe-265, Leu-268, and Val-269 of apoE are responsible for **hypertriglyceridemia** and also interfere with the formation of HDL. Substitutions of these residues by alanine provide a recombinant apoE form with improved biological functions.

Descriptors: *Apolipoproteins E--genetics--GE; * **Hypertriglyceridemia** --genetics--GE; *Mutation, Missense; Animals; Apolipoproteins E --administration and dosage--AD; **Cholesterol** --blood--BL; Humans; **Hypertriglyceridemia** --etiology--ET; Lipoproteins, HDL--biosynthesis--BI; Lipoproteins, VLDL--secretion--SE; Liver--secretion--SE; Mice; Mice, Knockout; Mutagenesis, Site-Directed; Peptide Fragments--administration and dosage--AD...

Chemical Name: Apolipoproteins E; Lipoproteins, HDL; Lipoproteins, VLDL; Peptide Fragments; Recombinant Proteins; Triglycerides; very low density lipoprotein triglyceride; **Cholesterol**

6/3,K/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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16034232 PMID: 15017358

Probing the pathways of chylomicron and HDL metabolism using adenovirus **-mediated gene transfer.**

Zannis Vassilis I; Chroni Angeliki; Kypreos Kyriakos E; Kan Horng-Yuan; Cesar Thais Borges; Zanni Eleni E; Kardassis Dimitris

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Current opinion in lipidology (England) Apr 2004, 15 (2) p151-66, ISSN 0957-9672 Journal Code: 9010000

Contract/Grant No.: HL48739; HL; NHLBI; HL68216; HL; NHLBI

Publishing Model Print

Document type: Journal Article; Review; Review, Tutorial

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

Probing the pathways of chylomicron and HDL metabolism using adenovirus **-mediated gene transfer.**

PURPOSE OF THE REVIEW: This review clarifies the functions of key proteins of the chylomicron and the HDL pathways. RECENT FINDINGS: **Adenovirus** -mediated gene transfer of several apolipoprotein (apo)E forms in mice showed that the amino-terminal 1-185 domain of **apoE** can direct receptor-mediated lipoprotein clearance in vivo. Clearance is mediated mainly by the LDL receptor. The carboxyl-terminal 261-299 domain of **apoE** induces **hypertriglyceridemia** , because of increased VLDL secretion, diminished lipolysis and inefficient VLDL clearance. **Truncated apoE** forms, including **apoE2** -202, have a dominant effect in remnant clearance and may have future therapeutic applications for the correction of remnant removal disorders. Permanent expression of **apoE** and apoA-I following **adenoviral** gene transfer protected mice from atherosclerosis. Functional assays, protein cross-linking, and **adenovirus** -mediated gene transfer of apoA-I mutants in apoA-I deficient mice showed that residues 220-231, as well as the central helices of apoA...

... and carboxyl-terminal deletion mutant formed discoidal HDL, and a carboxyl-terminal deletion mutant formed only pre-beta-HDL. The findings support a model of **cholesterol** efflux that requires direct physical interactions between apoA-I and ATP-binding cassette transporter A1, and can explain Tangier disease and other HDL deficiencies. SUMMARY: New insights are provided into the role of **apoE** in **cholesterol** and triglyceride homeostasis, and of apoA-I in the biogenesis of HDL. Clearance of the lipoprotein remnants and increase in HDL synthesis are obvious targets...

6/3,K/3 (Item 3 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

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14951679 PMID: 12950448

Lipoproteins produced by ApoE-/- astrocytes infected with adenovirus **expressing human ApoE.**

Peng Dacheng; Song Ching; Reardon Catherine A; Liao Shutsung; Getz Godfrey S

Department of Pathology, University of Chicago, Chicago, Illinois, USA.

Journal of neurochemistry (England) Sep 2003, 86 (6) p1391-402, ISSN 0022-3042 Journal Code: 2985190R

Contract/Grant No.: DK42086; DK; NIDDK; NS520138; NS; NINDS

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM
Record type: MEDLINE; Completed

Lipoproteins produced by ApoE-/- astrocytes infected with adenovirus **expressing human ApoE.**

We have developed an astrocyte cell culture system that is attractive for the study of **apoE** structure and its impact on astrocyte lipoproteins and neuronal function. Primary astrocytes from **apoE** -/- mice were infected with **adenovirus** expressing **apoE3** or □apoE4□ and the nascent lipoproteins secreted were characterized. The nascent **apoE** -containing astrocyte particles were predominantly the size of plasma high density lipoprotein (HDL). **ApoE4** , in contrast to **apoE3** , appeared to be distributed in two distinct lipoprotein peaks and the **apoE4** -containing lipoproteins contained significantly more radiolabeled triglyceride. On electron micrographs the astrocyte particles were both discoidal and spherical in shape with a prevalence of stacked discs in **apoE3** particles, but single discs and larger spheres in **apoE4** particles. The **apoE4** discs were significantly wider than **apoE3** discs. These properties of the astrocyte lipoproteins are similar to those obtained from **apoE** isoform transgenic mice. Astrocyte lipoproteins containing **apoE3** , but not **apoE4** , stimulated neurite outgrowth in Neuro-2a cells. These studies suggest that the isoform-specific effects of **apoE** lipoproteins may involve differences in particle size and composition. Finally we demonstrate the usefulness of this system by expressing a **truncated apoE3** (delta202-299) mutant and show preliminary data indicating that a liver X receptor agonist promotes HDL output by the astrocytes without an increase in **apoE** in the media. This cell culture system is more flexible and allows for more rapid expression of **apoE** mutants..

...; deficiency--DF; Apolipoproteins E--ultrastructure--UL; Astrocytes --cytology--CY; Astrocytes--drug effects--DE; Astrocytes--virology--VI; Cell Differentiation--drug effects--DE; Cell Fractionation; Cells, Cultured ; **Cholesterol** --analysis--AN; **Cholesterol** --metabolism--ME; Cholic Acids --pharmacology--PD; Humans; Lipoproteins, HDL--chemistry--CH; Lipoproteins, HDL--pharmacology--PD; Mice; Microscopy, Electron; Neurons --cytology--CY; Neurons--drug effects--DE...

Chemical Name: 3,6-dihydroxy-5-cholanoic acid-N-methyl-N-methoxy-24-amide ; Apolipoproteins E; Cholic Acids; Lipoproteins, HDL; Phospholipids; apolipoprotein E-3; apolipoprotein E-4; **Cholesterol**

6/3,K/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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14930039 PMID: 12924933

Molecular mechanisms of type III hyperlipoproteinemia: The contribution of the carboxy-terminal domain of ApoE can account for the dyslipidemia that is associated with the E2/E2 phenotype.

Kypreos Kyriakos E; Li Xiaoping; van Dijk Ko Willems; Havekes Louis M; Zannis Vassilis I

Molecular Genetics, Department of Medicine, Boston University School of Medicine, Boston, Massachusetts 02118-2394, USA.

Biochemistry (United States) Aug 26 2003, 42 (33) p9841-53, ISSN 0006-2960 Journal Code: 0370623

Contract/Grant No.: HL68216; HL; NHLBI

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

... has reduced affinity for the LDL receptor and is associated with type III hyperlipoproteinemia in humans. Consistent with these observations, we have found that following **adenovirus** -mediated gene transfer, full-length **apoE2** aggravates the hypercholesterolemia and induces **hypertriglyceridemia** in E-deficient mice and induces combined **hyperlipidemia** in C57BL/6 mice. Unexpectedly, the **truncated apoE2** -202 form that has an R158 for C substitution when expressed at levels similar to those of the full-length **apoE2** normalized the **cholesterol** levels of E-deficient mice without induction of **hypertriglyceridemia** . The **apoE2** truncation increased the affinity of POPC- **apoE** particles for the LDL receptor, and the full-length **apoE2** had a dominant effect in VLDL triglyceride secretion. **Hyperlipidemia** in normal C57BL/6 mice was prevented by coinfection with equal doses of each, the **apoE2** and the **apoE2** -202-expressing adenoviruses, indicating that **truncated apoE** forms have a dominant effect in remnant clearance. **Hypertriglyceridemia** was completely corrected by coinfection of mice with an **adenovirus** -expressing wild-type lipoprotein lipase, whereas an inactive lipoprotein lipase had a smaller effect. The findings suggest that the **apoE2** -induced dyslipidemia is not merely the result of substitution of R158 for C but results from increased secretion of a triglyceride-enriched VLDL that cannot undergo lipolysis, inhibition of LpL activity, and impaired clearance of chylomicron remnants. Infection of E(-)(/)(-)xLDLr(-)(/)(-) double-deficient mice with **apoE2** -202 did not affect the plasma **cholesterol** levels, and also did not induce **hypertriglyceridemia** . In contrast, **apoE2** exacerbated the hypercholesterolemia and induced **hypertriglyceridemia** , suggesting that the LDL receptor is the predominant receptor in remnant clearance.

; Adenoviridae--genetics--GE; Animals; Apolipoproteins E--deficiency--DF; Apolipoproteins E--genetics--GE; Biological Transport, Active--genetics --GE; CHO Cells; **Cholesterol** --blood--BL; Genes, Dominant; Hamsters; Humans; **Hyperlipidemia** --pathology--PA; Hyperlipoproteinemia Type III --pathology--PA; Lipolysis; Lipoprotein Lipase--genetics--GE; Lipoprotein Lipase--metabolism--ME; Lipoproteins, VLDL--secretion--SE; Liver --metabolism--ME; Mice; Mice...

Chemical Name: Apolipoproteins E; Lipoproteins, VLDL; Phosphatidylcholines; Receptors, LDL; Triglycerides; apolipoprotein E-2; **Cholesterol** ; 1-palmitoyl-2-oleoylphosphatidylcholine; Lipoprotein Lipase

6/3,K/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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14836078 PMID: 12809509
The role of human and mouse hepatic scavenger receptor class B type I (SR-BI) in the selective uptake of low-density lipoprotein-cholesteryl esters.

Rhainds David; Brodeur Mathieu; Lapointe Jany; Charpentier Daniel; Falstrault Louise; Brissette Louise

Departement des Sciences Biologiques, Universite du Quebec a Montreal, Montreal, Quebec, Canada H3C 3P8. david.rhainds@internet.uqam.ca

Biochemistry (United States) Jun 24 2003, 42 (24) p7527-38, ISSN 0006-2960 Journal Code: 0370623

Publishing Model Print

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: MEDLINE; Completed

... 0.05) and CE selective uptake by more than 85% (p < 0.01) for both ligands. Second, HepG2 cells were stably transfected with a eukaryotic **vector** expressing a 400-bp human SR-BI antisense cDNA **fragment** . Clone 17 (C17) has a 70% (p < 0.01) reduction in SR-BI expression. In this clone, (3)H-CE-LDL and (3)H-CE...
... and other pathways for 11%. CE selective uptake from LDL and HDL(3) is likely to occur in the liver, since unlabeled HDL (total and **apoE** -free HDL(3)) and LDL, when added in physiological proportions, only partially competed for LDL- and HDL(3)-CE selective uptake. In this setting, human hepatic SR-BI may be a crucial molecule in the turnover of both LDL- and HDL(3) **cholesterol** .
Descriptors: *Antigens, CD36--metabolism--ME; * **Cholesterol** Esters --metabolism--ME; *Lipoproteins, LDL--metabolism--ME; *Lipoproteins, LDL **Cholesterol** --metabolism--ME; *Liver--metabolism--ME; *Membrane Proteins
Chemical Name: Antibodies, Monoclonal; Antigens, CD36; **Cholesterol** Esters; Iodine Isotopes; Lipoproteins, LDL; Lipoproteins, LDL **Cholesterol** ; Membrane Proteins; Scarb1 protein, mouse; scavenger receptors; Tritium

6/3,K/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2005 Dialog. All rts. reserv.

14654260 PMID: 12576523
Hyperlipidemia **in** APOE2 **transgenic mice is ameliorated by a** truncated apoE variant□ lacking the C-terminal domain.□
Gerritsen Gery; Kypreos Kyriakos E; van der Zee Andre; Teusink Bas; Zannis Vassilis I; Havekes Louis M; van Dijk Ko Willems
Department of Human Genetics, Leiden University Medical Center, The Netherlands.
Journal of lipid research (United States) Feb 2003, 44 (2) p408-14, ISSN 0022-2275 Journal Code: 0376606
Contract/Grant No.: HL 68216; HL; NHLBI
Publishing Model Print-Electronic
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

Hyperlipidemia **in** APOE2 **transgenic mice is ameliorated by a** truncated apoE variant□ lacking the C-terminal domain.□
Familial dysbetalipoproteinemia associated with the apolipoprotein E2 (**APOE2**) genotype is a recessive disorder with low penetrance. We have investigated whether additional expression of full-length **APOE3** , **APOE4** , or a **truncated variant** of **APOE4** (□APOE4□ -202) can reduce□APOE2□ -associated **hyperlipidemia** . This was achieved using **adenovirus** -mediated gene transfer to mice transgenic for human **APOE2** and deficient for endogenous **Apoe** (**APOE2** .□Apoe□ -/- mice). The□hyperlipidemia□of□APOE2□ . **Apoe** -/- mice was readily aggravated by **APOE3** and □APOE4□ overexpression. Only a very low dose of **APOE4** **adenovirus** was capable of reducing the serum **cholesterol** and triglyceride (TG) levels. Expression of higher doses of **APOE4** was associated with an increased VLDL-TG production rate and the accumulation of TG-rich VLDL in the circulation. In contrast, a high dose of **adenovirus** carrying **APOE4** -202 reduced both the **cholesterol** and TG levels in **APOE2** .□Apoe□ -/- mice. Despite the absence of the C-terminal lipid-binding domain, **APOE4** -202 is apparently capable of binding to lipoproteins and mediating hepatic uptake. Moreover, overexpression of **APOE4** -202 in **APOE2** .□Apoe□ -/- mice does not aggravate their **hypertriglyceridemia** . These results extend our previous analyses of **APOE4** -202 expression in **Apoe** -/- mice and demonstrate that

apoE4 -202 functions even in the presence of clearance-defective **apoE2** . Thus, **apoE4** -202 is a safe and efficient candidate for future therapeutic applications.

Descriptors: *Apolipoproteins E--genetics--GE; *Apolipoproteins E --metabolism--ME; * **Hyperlipidemia** --metabolism--ME; *Protein Isoforms --genetics--GE; *Protein Isoforms--metabolism--ME; Adenoviridae--genetics --GE; Adenoviridae--metabolism--ME; Animals; Apolipoproteins E--chemistry --CH; **Cholesterol** --blood--BL; Humans; **Hyperlipidemia** --genetics--GE; Lipids--blood--BL; Lipoproteins--blood--BL; Lipoproteins, VLDL--chemistry --CH; Lipoproteins, VLDL--metabolism--ME; Liver--metabolism--ME; Mice; Mice, Transgenic; Protein Isoforms--chemistry...

Chemical Name: Apolipoproteins E; Lipids; Lipoproteins; Lipoproteins, VLDL; Protein Isoforms; Triglycerides; apolipoprotein E-2; apolipoprotein E-4; very low density lipoprotein triglyceride; **Cholesterol**

?

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Set     Items   Description
S1       1855   (TRUNCATED OR VARIANT OR FRAGMENT OR DELETED) (S) (APOE OR
            APOE? OR (APOLIPOPROTEIN (W) E))
S2        569   S1 AND (HYPERLIPIDEMIA OR CHOLESTEROL OR HYPERTRIGLYCERIDE-
            MIA)
S3         39   S2 AND (VECTOR OR ADENOVIRUS OR ADENOVIRAL OR PLASMID)
S4         23   RD (unique items)
S5         17   S4 NOT PY>2001
S6          6   S4 NOT S5
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COST
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               $3.08  14 Type(s) in Format  3
            $3.08  14 Types
     $5.10  Estimated cost File155
            $2.96    0.501 DialUnits File5
               $0.80  5 Type(s) in Format 95 (KWIC)
            $0.80  5 Types
     $3.76  Estimated cost File5
            $4.50    0.424 DialUnits File73
              $11.76  4 Type(s) in Format  3
           $11.76  4 Types
    $16.26  Estimated cost File73
            OneSearch, 3 files,  1.518 DialUnits FileOS
     $1.33  INTERNET
    $26.45  Estimated cost this search
    $27.28  Estimated total session cost   1.746 DialUnits
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